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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/646,798 | 08/25/2003 | Anurag Rathore | 161765.00520 | 3621 |
| 28523 | 7590 | 09/17/2008 | | |
| PFIZER INC. PATENT DEPARTMENT, MS8260-1611 EASTERN POINT ROAD GROTON, CT 06340 | | | EXAMINER GUDIBANDE, SATYANARAYAN R | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1654 | |
| | | | NOTIFICATION DATE | DELIVERY MODE |
| | | | 09/17/2008 | ELECTRONIC |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

| | | | |
|------------------------------|--------------------------------------------------|---------------------------------------|--|
| Office Action Summary | Application No. 10/646,798 | Applicant(s) RATHORE ET AL. | |
| | Examiner SATYANARAYANA R. GUDIBANDE | Art Unit 1654 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 and 39-76 is/are pending in the application.
- 4a) Of the above claim(s) 69-76 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-34 and 39-68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I invention in the reply filed on October 3, 2005 is acknowledged. The traversal arguments were addressed in the non-final rejection dated 11/29/05.

Applicant's request to rejoin claims 69-76 has been denied on the basis that the currently amended claims 69-76 does not further limit the invention in base claim 1. Because, claim 69 is drawn to growth hormone antagonist polypeptide is broader in scope than the instant claim 1 that is drawn to a process of decreasing the impurity of polypeptide B-2036.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/30/08 has been entered.

Applicants remarks in the response filed on 5/30/08 have been acknowledged.

Claims 1-34 and 39-76 are pending.

Claims 69-76 have been withdrawn from further consideration as being drawn to non-elected invention.

Claims 1-34 and 39-68 are examined on the merit.

Any objections and/or rejections made in the previous office action dated 12/7/07 and not specifically mentioned here are considered withdrawn.

Withdrawn Rejections

Applicant's arguments see pages 11-13, filed 5/30/08, with respect to the rejection(s) of claim(s) 1-34 and 39-68 under obviousness have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of new prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 4 recites the limitation "purifying" and "purified" in line 3 of claims 3 and 4 respectively. There is insufficient antecedent basis for this limitation in the claim. Because, claim 2 from which it claims 3 and 4 depend from do not recite the term "purify". Also, claim 1 only recites the term "decreasing the amount of **an** impurity". Decreasing the amount of **an** impurity in a protein isolation step among many (all) impurities present in the protein isolation step does not amount purification of the protein.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a limitation “decreasing the amount of an impurity”. The term does not clearly identify “by how much?” for e.g., by 50% or 60% or “compared to what other impurity”. The claim as recited imply that even after contacting with the mercapto compound the impurity is still present in the protein preparation. Therefore, the claim is being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-12, 17, 18, 39, 40, 57 and 58 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-12, 17, 18, 39, 40, 57 and 58 recite the term “at least about”. MPEP 2173.05 states that “[t]he court held that claims reciting “at least about” were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term “about.”

Claims 19-22, 31-34, 41-56 and 59-68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The claims recite a terms “from about” and “to about” two dynamic ranges to describe the lower and upper range for concentration of the cysteine (claims 19-22, 41 and 42), concentration of the Tris buffer (claims 31-34), concentration of the B-2036 (claims 43-48), concentration of the pH (claims 49-52), temperature (claims 55 and 56), time (claims 57-62) and buffer volume (63-68). The terms provide two different scopes of the claimed subject matter- both defining a dynamic boundaries. "About" is a term that allows variability, i.e.- about 30 minutes can span, e.g., 20-40 minutes, while "within 30 minutes" or "up to 30 minutes" or "less than 30 minutes" exclude any time point beyond 30 minutes and define a static boundary. Because the claims define two dynamic boundaries with varying scopes, the claims are indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-34 and 39-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/24157 of Sorensen in view of US 5,849,535 issued to Cunningham.

In the instant application, applicants claim a process for decreasing trisulfide impurity in recombinant production of a growth hormone antagonist polypeptide B-2036 **of** (SEQ ID NO: 1) in genetically modified host cells. The steps involved in reducing the trisulfide impurity during the process involved contacting the impurity with a mercapto compound, growing the host cells to produce the polypeptide, purifying the polypeptide and pegylating the polypeptide.

The reference of Sorensen discloses a method for detecting the presence of hydrophobic derivative of a growth hormone and a method for converting the derivative into native form (page 1, lines 5-8). The reference also teaches that the growth hormone is obtained by the recombinant technology (page 2, lines 14-19) and authors were able to identify a hydrophobic impurity present in the isolated growth hormone using hydrophobic interaction chromatography (HIC) (page 3, lines 1-10). Further, the hydrophobic impurity was identified as a growth hormone derivative that contained one disulfide bridge (Cys 53-Cys 165) and one trisulfide bridge (Cys 182-Cys 189) (page 7, lines 11-16). The reference also discloses that a process is needed that will ensure a quantitative conversion of the hydrophobic derivative of growth hormone (GH) directly into the native product (page 3, lines 22-24). The reference further teaches that treatment of the hydrophobic derivative of human growth hormone with a mercapto compound would convert it to native form (page 4, lines 28-30) and the treatment can be carried out in a solvent. The reference also teaches other mercapto compounds such as cysteine,

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glutathione, 2-mercaptoethanol, dithiothreitol, etc., as suitable reagents for the conversion (page 5, lines 18-27). This reads on instant claims 1-12. The reference also teaches that it is preferred to treat the whole batch of the growth hormone (with the mercapto compound) comprising the hydrophobic derivative of hGH directly without isolating the growth hormone derivative (page 5, lines 15-17) implying that the method can be practiced with the cell culture medium without purification of the hGH. The reference teaches preferred concentration of cysteine as 0.5 to 3 mM that is within the range recited in instant claims 17-22, 39 and 40. The reference lists several buffer solution and tris being the preferred with a pH range from 5 to 10 (page 6, lines 23-31). This reads on instant claims 13-16, 23-34 and 49-52.

The reference of Sorensen does not teach that the growth hormone B2036 of (SEQ ID NO: 2) and pegylation of the B2036.

It should be noted that the instant claims recite B2036 of (SEQ ID NO:2) and hence it is not drawn to SEQ ID NO: 2 per se.

Cunningham, et al., discloses a method for the preparation human growth hormone antagonist, B-2036 variants (example V in columns 56-61), that encompass the pegylation of the growth hormone (column 64). The described method meets the limitations of the 10-50 mM tris buffer temperature, pH (column 59), and volume of the buffer used during the process (column 58). The reference the GH variant 2036 was constructed rendering the variant better a better candidate for modification with PEG while **preserving enhanced affinity of the variant for its receptors** (column 55, lines 39-48). The 2036 variant has the following substitutions:

H18D, H21N, G120K, R167N, K168A, D171S, K172R,
E174S, I179T.

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The above substitutions in hGH to obtain the B2036 variant suggest that the rest of the hGH sequence remains the same in B2036 including the ones that forms one disulfide bridge (Cys 53-Cys 165) and one trisulfide bridge (Cys 182-Cys 189) bridge. The reference also teaches that the hGH variants including B2036 were purified by hydrophobic interaction chromatography (HIC) (column 20, lines 30-42). It should be noted that the receptor binding activity shows an enhancement and the Cysteine residues at positions 182 and 189 have not been substituted. Therefore the tertiary structure of the variant protein 2036 is comparable to the unmodified GH.

It would have been obvious to one of ordinary skill the art to combine the teachings of Sorensen and Cunningham to arrive at the instant invention. Because, the B2036 is a variant of hGH comprising the cysteine residues that forms the disulfide and trisulfide bridges. The Cunningham reference teaches that the hGH variants including B2036 were purified by hydrophobic interaction chromatography (HIC). This is indicative of the fact mentioned in the reference of Sorensen that the growth hormones were purified by HIC to remove the hydrophobic derivative impurity. This clearly implies that the preparation of Cunningham contained the hydrophobic derivative which is the trisulfide derivative of the B2036. The motivation to combine the teachings comes from the fact that Sorensen teaches that a process is needed that will ensure a quantitative conversion of the hydrophobic derivative of growth hormone (GH) directly into the native product. The reference further teaches that treatment of the hydrophobic derivative of human growth hormone with a mercapto compound would convert it to native form. There would have been reasonable expectation of success given the fact that Sorensen had successfully used the method of treating the trisulfide impurity in hGH with a mercapto compound to convert it into native form and hence the same would be applicable to

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B2036 a variant of hGH wherein the disulfide and trisulfide bond forming cysteine residues are present.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654